Doc Code: AP.PRE.REQ

PTO/SB/33 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)	
10913.0002-00000	

Application Number	Filed
10/522,087	July 26, 2005

First Named Inventor	
Steffen GOLETZ	

Art Unit	Examiner
1643	Hong SANG

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- ☐ applicant/inventor.
- ☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- ☑ attorney or agent of record. Registration number 61,169.
- ☐ attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____

Signature

Laurence A. Shumway
Typed or printed name

617.452.1689
Telephone number

November 6, 2009
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☑ *Total of 1 forms are submitted.

PATENT
Attorney Docket No. 10913.0002-00000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)
Steffen GOLETZ	) Group Art Unit: 1643
Application No.: 10/522,087	) Examiner: Hong SANG
Filed: July 26, 2005	) Confirmation No.: 7596
For: METHOD FOR THE PRODUCTION OF AN IMMUNOSTIMULATING MUCIN (MUC1)	)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

PRE-APPEAL BRIEF REQUEST FOR REVIEW

In response to the Final Office Action dated June 23, 2009, and further to the Advisory Action mailed October 6, 2009, Applicants respectfully submit this Pre-Appeal Brief Request for Review in conjunction with a Notice of Appeal under 37 C.F.R. §41.31, appeal fee payment, and form PTO/SB/33. Applicants request this Pre-Appeal Brief Conference in accordance with the guidelines set forth in the Official Gazette Notice of July 12, 2005.

The period for filing this request has been extended to November 6, 2009 by the accompanying Petition for Extension of Time of one month, and payment of the required fee. Applicants' Response to the Final Office Action was filed on August 24, 2009 (August 23 was a Sunday), which was within two months of the mailing date of the final Office Action. The Examiner's Advisory Action reset the shortened statutory period for reply since it was mailed October 6, 2009, which is after the three month shortened statutory period.

REMARKS

Claims 1, 2, 9, and 10 are pending and under examination.

Clear error is present in the rejection of claims 1, 2, 9, and 10 under 35 U.S.C. § 103(a) as allegedly obvious over Snijdewint *et al., Cancer Immunol. Immunother.* 48:47-55 (1999) (*Snijdewint*), in view of Ryuko *et al., Tumor Biol.* 21:197-210 (2000) (*Ryuko*), Torabi-Pour *et al., Biomed Chromatogr.* 15:18-24 (2001) (*Torabi-Pour*), U.S. Patent No. 4,939,240 by Chu *et al.* (*Chu*), and U.S. Patent No. 7,402,403 to Robertson *et al.* (*Robertson*). Applicants respectfully submit that the outstanding rejection disregards the instructions of the M.P.E.P. and Courts to view the invention as a whole and not base rejections merely on the differences between the cited references and the claims. The rejection further fails to provide the explicit reasoning necessary to support combining or modifying references or to demonstrate that there would be a reasonable expectation of success in doing so. Finally, the Examiner has not fully considered the cited references, particularly the primary references *Snijdewint* and *Ryuko*.

The claimed invention

The claims are directed to methods of producing or identifying MUC1 molecules able to generate an immune response in humans. The methods entail contacting a mixture of MUC1 molecules with an antibody that, *inter alia*, binds "a MUC1 fragment ...[where the binding] is made possible or [is] increased by glycosylation of the threonine of a PDTR sequence." The claims also recite that the mixture of MUC1 molecules is expressed and/or secreted by a cell line that expresses and/or secretes tumor associated MUC1, or is a lysate of such a cell line.

Rejection under 35 U.S.C. § 103(a)

The Examiner alleges that *Snijdewint* reports isolating a MUC1 preparation from the supernatant of the breast cancer cell line ZR-75-1 by affinity binding to the MUC1 antibody 139H2. *Ryuko* was cited to allegedly demonstrate that the 139H2 antibody used by *Snijdewint* binds the same MUC1 epitope and has similar reactivity patterns as the A76-A/C7 antibody. The Examiner then concluded that it would have been obvious to substitute one known antibody for another equivalent antibody to allegedly arrive at Applicants claimed methods. *Torabi-Pour, Chu,* and *Robertson*, were cited for allegedly

disclosing isolating an antigen from a cell lysate and formulating it in a diagnostic or pharmaceutical form. These references will not be discussed further in this paper, and Applicants respectfully submit that they do not remedy the collective failures of *Snijdewint* and *Ryuko*, for the reasons of record. *See, e.g.*, pages 13 and 14 of the Response filed August 24, 2009.

Snijdewint

Snijdewint does not teach or suggest methods of producing or isolating MUC1 molecules which are *able to generate an immune response in humans*. As Applicants have previously argued, *Snijdewint* merely reports diagnostic assays that reveal *pre-existing* "MUC-1-antigen-specific T cells in the blood of [some] ovarian cancer patients...." *Snijdewint* at 51, right column, first full paragraph. As Applicants demonstrated in the last Response, because *Snijdewint* teaches that PBMCs isolated from healthy donors (which would not be expected to contain pre-existing MUC1-antigen-specific T cells) did not proliferate in response to this MUC1, any MUC1 molecules isolated by *Snijdewint's* methods would not be expected to *generate* an immune response, as required by the claims. *See Snijdewint* at 49 "Effect of MUC1 on PBMC proliferation." The marginal effect of MUC-1 on T cells in three out of twelve cancer patients—where some pre-existing MUC1-antigen-specific T cells might be expected—led the authors to conclude that "[t]he weak proliferative responses we found made it *impossible* to find positive or negative correlations [of humoral responses to MUC1 with cellular responses to MUC1 and its tandem repeats]." *Snijdewint* at 53, left column, second full paragraph (emphasis added). The MUC-1 molecules produced by *Snijdewint's* methods were even shown to be *immunosuppressive*. *See Snijdewint* at 49, right column and Figure 4.

At best, the skilled artisan considering *Snijdewint* would consider it a diagnostic report for detecting pre-existing MUC-1 immune reactivity in patients and have no motivation to use it as a basis for methods to produce or isolate MUC1 molecules able to generate an immune response in humans. *Snijdewint's* reports of either no effect or an immunosuppressive effect of the MUC-1 isolated by their methods stand in contrast to the examples in the application, which show that MUC1 produced according to the methods of the invention is both immunostimulatory (*see* Example 5B) and can

generate a MUC1-specific cytotoxic immune response in *naïve* immune cells (*see* Example 7).

Ryuko

In the Final Office Action, the Examiner relied on *Ryuko* to suggest that the 139H2 antibody used by *Snijdewint* is an obvious variant of the A76-A/C7 antibody because they allegedly share some binding properties and that it would be obvious to substitute them with predictable results. In response, Applicants demonstrated that *Ryuko* actually provides evidence to the contrary, showing that the 139H2 antibody of *Snijdewint* does not bind "a MUC1 fragment ...[where the binding] is made possible or [is] increased by glycosylation of the threonine of a PDTR sequence," as recited in Applicants' claims. *See* top panel of Figure 2 in *Ryuko* (showing that 139H2 does not distinguish between glycosylated and non-glycosylated antigens).

In the Advisory Action, the Examiner appears to concede that the 139H2 and A76-A/C7 antibodies are not obvious variants, but now simply argues that "it is obvious from the teachings of the cited references to modify the method of Snijdewint et al. to use the monoclonal antibodies disclosed by Ryuko to isolate MUC1 antigens...." The only motivation for such a substitution proffered by the Examiner is that the antibodies listed by *Ryuko* react with MUC-1 expressing cancer cell lines and "glycosylated MUC1 peptides may be better agents for immunotherapy than non-glycosylated ones," citing to Page 208, column 2 of *Ryuko.* This passage in Ryuko, however, merely states that "MAbs directed towards the glycosylated PDTR region *may help to elucidate the role of glycosylation* in the antigenicity of this dominant site through the changes induced on the three-dimensional configuration of the epitope." *Ryuko* at 208, right column, emphasis added. Therefore, far from suggesting that antibodies that differentiate between glycosylated and non-glycosylated forms of MUC1 are somehow more desirable, *Ryuko* simply invites investigation as to what the role MUC-1 glycosylation plays for immunogenicity of MUC1. This passage, and *Ryuko* as a whole, offers no motivation to modify *Snijdewint's* teachings—which again, are limited to detecting pre-existing MUC1 immune responses.

Simply put, the skilled artisan considering the report of diagnostic assays in *Snijdewint*—which showed no effect of isolated MUC-1 on the naïve T-cells of healthy

patients—would have no basis for arriving at methods to produce or identify MUC-1 molecules that generate an immune response, let alone then substituting *any* of the antibodies in *Ryuko* in such methods, and then selecting an antibody with the features recited in Applicants' claims—***absent Applicants' disclosure***.

Accordingly, Applicants respectfully submit that the outstanding rejection under 35 U.S.C. § 103(a) is clearly improper and should be withdrawn.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: November 6, 2009

By: _____
Laurence A. Shunway
Reg. No. 61,169
617.452.1689